Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-124 are pending in this application and are rejected on various grounds. Claims 124 has been canceled without prejudice or disclaimer to pursue their subject matter in subsequent applications.

Applicants note that in the instant Office Action, the SEQ ID NO: 223 of PRO 809 was erroneously referred to, in some instances, as SEQ ID NO: 259 or SEQ ID NO: 12. This is an obvious error. Thus, any reference made to the above mentioned sequence identifiers, in the Examiner's office action dated June 4, 2004, should be replaced with the correct SEQ ID NO: 223.

The rejections to the presently pending claims are respectfully traversed.

Formal Matters

The title of the invention has been amended to more particularly claim what the Applicants considers as their invention.

Information Disclosure Statement

Applicants submit an IDS separately enlisting references recited in the Blast report in order to be compliant with 37 C.F.R. § 1.98(a)(1). Consideration of this Information Disclosure Statement is respectfully requested.

Priority Determination

Applicants rely on the gene amplification assay for patentable utility which was first disclosed in U.S. Provisional Application 60/141,037, filed June 23, 1999, priority to which has been claimed in this application. Hence, Applicants should be entitled to at least an effective filing date of **June 23, 1999.**

Claim Rejections – 35 USC § 101 and 112, First paragraph

Claims 119-124 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility."

Claims 119-124 are further rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility, one skilled in the art clearly would not know how to use the claimed invention."

The Examiner asserts that "there is no disclosure of any disease or condition or analytical assay that could be performed using the claimed nucleic acids". The Examiner further specifically notes that "it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased polypeptide expression, such that the claimed polypeptides would be useful for diagnosis of cancer or as a drug target" and quotes an exemplary reference like Pennica *et al.* to show that "data pertaining to PRO809 nucleic acids do not necessarily indicate anything significant regarding the claimed PRO809 polypeptides". For the reasons outlined below, Applicants respectfully disagree.

Utility Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be

careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance with the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the (A)pplicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the Applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

To overcome the presumption of truth based on an assertion of utility by the Applicant, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. **Absolute predictability is not a requirement.** Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the applicant. The issue will then be decided on the totality of evidence.

A *prima facie* case of lack of utility has not been established

Applicants submit that the cancellation of claims 124 without prejudice or disclaimer, renders this rejection moot to these claims. As mentioned above under the section of priority, Applicants rely on the data presented in the gene amplification assay for patentable utility for this case. As the Examiner has noted, PRO809 gene is amplified 1.05 -1.61, that is, **2.070 to 3.053**

fold amplification, which is significant, according to the attached Declaration by Audrey Goddard, Ph.D., an expert in the gene amplification assay and co-inventor of this application.

Further, regarding the Examiner's rejection that there is a lack of correction of gene amplification data based on aneuploidy, Applicants submit that, as rightly noted by the Examiner and the Sen article, aneuploid tissues are **cancerous or pre-cancerous**. The present invention is directed to nucleic acids useful in the detection of cancer, irrespective of the mechanism by which gene amplification occurs. Even if the presence aneuploid cells or tissues were to predict a propensity towards cancer, the instant nucleic acids are still useful as diagnostic tools. Applicants have further included a declaration by Avi Ashkenazi, Ph.D., a co-inventor of this application, who says that:

> "An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes."

Therefore, a person of skill in the art would certainly consider the gene amplification results as significant and diagnostic for lung tumors.

Further, regarding the Examiner's assertion that increases in gene copy number do not reliably correlate with increased gene expression or polypeptide expression based on exemplary literature reports like Pennica *et al.* Applicants present declarations and articles to support their position that "it is more likely than not" that nucleic acid amplification correlates well with protein overexpression, for most genes.

According to the Examiner, Pennica *et al.* teaches that "An analysis of *WISP*-1 gene amplification and expression in human colon tumors **showed a correlation between DNA amplification and over-expression**, ... In contrast, *WISP*-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." (Emphasis added). Firstly, Applicants draw the Examiner's attention to Pennica's showing that "a correlation between DNA

amplification and over-expression existed for the *WISP*-1 gene" in 84% of the tumors examined. While Pennica discloses a lack of correlation for the *WISP*-2 gene, Pennica teaches nothing regarding such a lack of correlation in most genes in general. That is, Pennica's teachings are specific for the *WISP* family of genes, and are not directed to genes in general. The Utility Guidelines requires that for a *prima facie* showing of lack of utility, the Examiner has to provides evidence that it is **more likely than not** that a lack of correlation between protein expression and gene amplification exists, in general. Accordingly, Applicants respectfully submit that Pennica teaching cannot be used as *prima facie* evidence for the "more likely than not" standard as it teaches nothing of the correlation between gene amplification and polypeptide over-expression in genes in general.

In fact, contrary to what the Examiner contends, the art indicates, as discussed below, that if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. As noted even in Pennica *et al.*, a correlation between DNA amplification: polypeptide over-expression was observed in the case of *WISP-1*. Since the standard is not absolute certainty, a *prima facie* showing of lack of utility has not been made in this instance.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Applicants submit further exemplary articles to show that, contrary to what the Examiner asserts, the art indicates that, generally, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. For example, Orntoft *et al.* (Mol. and Cell. Proteomics, 2002, Vol.1, pages 37-45) studied transcript levels of 5600 genes in malignant bladder cancers many of which were linked to the gain or loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (Cancer Res., 2002, Vol. 62, pages 6240-45) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent

global influence of copy number changes on gene expression levels." (see page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.,* (PNAS, 2002, Vol. 99, pages 12963-12968) who studied a series of primary human breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

In addition, enclosed is a Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in humans. The scientists working on the project extensively rely on results of microarray experiments in their effort to identify such markers. As Dr. Polakis explains, using microarray analysis, Genentech scientists have identified approximately 200 gene transcripts (mRNAs) that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. To date, they have generated antibodies that bind to about 30 of the tumor antigen proteins expressed from these differentially expressed gene transcripts and have used these antibodies to quantitatively determine the level of production of these tumor antigen proteins in both human cancer cells and corresponding normal cells. Having compared the levels of mRNA and protein in both the tumor and normal cells analyzed, they found a very good correlation between mRNA and corresponding protein levels. Specifically, in approximately 80% of their observations they have found that increases in the level of a particular mRNA correlates with changes in the level of protein expressed from that mRNA. While the proper legal standard is to show that the existence of correlation between mRNA and polypeptide levels is more likely than not, the showing of approximately 80% correlation for the molecules tested in the Polakis Declaration greatly exceed this legal standard. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for human genes, increased mRNA levels typically correlate with an increase in abundance of the

encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology, that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the vast majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.,* Hyman *et al.,* Pollack *et al.,* and the Polakis declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO809 gene, that the PRO809 protein is concomitantly overexpressed. Thus, Applicants submit that the PRO809 proteins and nucleic acids have utility in the diagnosis of lung cancer and based on such a utility, one of skill in the art would know exactly how to use the protein for diagnosis of cancer.

Even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of evidence

Assuming *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, which Applicants submit is not true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a credible, specific and substantial utility. In support, Applicants submit a Declaration by Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the instant application. Dr. Avi Ashkenazi's Declaration explains that:

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Applicants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also the patient need not be exposed to the side effects associated with such agents.

This is further supported by the teachings of the attached article by Hanna and Mornin. The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

Thus, Applicants have demonstrated a credible, specific and substantial asserted utility for the PRO809 polypeptide, for example, in detecting the over-expression or absence of expression of PRO809. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed antibodies.

Hence, these data clearly support a role for PRO809 as a lung tumor marker. Thus, Applicants request that the present 35 U.S.C. §101 and §112, first paragraph rejections to the pending claims be withdrawn.

Claim Rejections – 35 USC § 112, second paragraph

Claims 122 and 124 are rejected under 35 U.S.C. §112, second paragraph for being indefinite.

Without acquiescing to the propriety of this rejection, Applicants have canceled Claim 124 and amended Claim 122 to recite "specifically binds." Further, Applicants submit that the

art-recognized meaning of "specifically binds" is that the antibody binds to a particular antigen and does not significantly cross-react with another antigen. Thus, Applicants respectfully request that this rejection be withdrawn.

Claim Rejections – 35 USC § 102

Claim 119 and 124 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 2001 42451-A1 (dated 6/2001).

As discussed under priority and based on the arguments presented for the utility of PRO809, Applicants believe they are entitled to at least an effective filing date of **June 23, 1999** which predates the cited reference. Hence, WO 2001 42451-A1 is not prior art under 102(a) or any other section of 35 U.S.C. §102. Hence, Applicants respectfully request that this rejection be withdrawn.

Claim Rejections – 35 USC § 103(a)

Claims 119, 120, 123 and 124 are rejected under 35 U.S.C. 103(a) as being unpatentable over clone H74302 isolated by Hillier *et al.* (1995) in view of Sibson, WO94/01548.

H74302 (582 nucleotides) has 58.66% similarity to SEQ ID NO: 222 defined in the claims. Even in the 562 nucleotide region where the two sequences overlap, only 503 nucleotides match, which translates to 89.50 percent similarity. Further, only antibodies that specifically bind to SEQ ID NO: 222 are claimed in the instant application. Thus, H74302 does not anticipate all the elements of claims 119, 120, 123 and therefore, is not a 103(a) reference. Since the primary reference, H74302 does not teach all the elements of the pending claims and neither does Sibson, this rejection falls. Hence, this rejection should be withdrawn.

Claims 121 and 122 are rejected under 35 U.S.C. 103(a) as being unpatentable over clones H74302, H74303, H58326, H73373 and RO2548 isolated by Hillier *et al.* (1995) in view of Sibson, WO94/01548 and further, in view of U.S. Patent 5,565,332 (Hoogenboom) in case of claim 121, or in view of U.S. Patent 4,946,778 (Ladner) in case of claim 122.

As discussed above, H74302 has 58.66% similarity to SEQ ID NO: 222 and does not anticipate all the elements of claims 119, 120, 123 and therefore, is not a 103(a) reference. Clone H74303 has 41.73% overall similarity (414 out of 992 nucleotides) to SEQ ID NO: 222, H58326 has 42.14% overall similarity (418 out of 992 nucleotides) to SEQ ID NO: 222, H73373 has 48.39% overall similarity (480 out of 992 nucleotides) to SEQ ID NO: 222 and RO2548 has 38.2% overall similarity (379 out of 992 nucleotides) to SEQ ID NO: 222, defined in the instant claims. Further, only antibodies that specifically bind to SEQ ID NO: 222 are claimed in the instant application. Thus, clones H74302, H74303, H58326, H73373 and RO2548 do not anticipate the elements of claims 122-126, 129-131 and 135-138 and therefore, are not 103(a) references.

Since the primary reference(s) not teach all the claimed elements, and neither do Sibson, Hoogenboom or Ladner, this rejections falls. Accordingly, this rejection should be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C16). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: November 4, 2004

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